that with this submission, the rejection of claims 1-14 under 35 USC 112, first paragraph, would be withdrawn.

Claims 1, 2, 4, 5, 7-10 and 12-14 stand rejected under 35 USC 103 as allegedly being obvious over Gillies et al. The rejection is traversed for the reasons that follow.

The present invention relates to a process for the production of a recombinant primate antibody. The claimed process requires the use of cDNA encoding the entire constant and variable regions of both the antibody heavy and light chains. By contrast, Gillies teaches the use of cDNA coding for the variable region of the heavy chain but genomic DNA coding for the constant region of the heavy chain.

Dr. Lewis explains in detail in the Declaration filed January 25, 1996, why it would not have been obvious, in view of the art, to make recombinant antibodies according to the present method (in considering the comments that follow, the Examiner is urged to take note of Attachment A of the Lewis Declaration). Dr. Lewis indicates in paragraph 7 of his Declaration that, at the time of the present invention, it was thought necessary to remove the poly A sequence of the antibody heavy and light chain

genes prior to expressing them. This was believed to be the case since proper mRNA 3' end formation was understood to be controlled by a consensus sequence located a specified distance from a poly A site. It was clear that insertion of a poly A-containing sequence into a vector that had its own poly A sequence and consensus region would alter the distance between the consensus and first poly A sequences. In addition, it was believed desirable to also remove instability sequences present in the 3' untranslated regions of RNA to ensure efficient high level expression.

For the sequence encoding the light chain of the antibody, a restriction enzyme could be used in a partial digest to remove the poly A sequence as well as the preceding 3' untranslated sequences in the constant region DNA. For the constant region of the heavy chain, however, no restriction enzyme recognition sites exist to allow cleavage of the sequence to remove the 3' untranslated sequence and the poly A site. As a result, Gillies et al grafted genomic DNA encoding the heavy chain constant region to cDNA encoding the variable region of the heavy chain of the antibody of interest.

The present invention results from Applicants' surprising finding that, in fact, the entire cDNA, including the polyadenylation sequence and preceding untranslated region, was suitable for expression of both the heavy and light chains of an antibody. This finding provided a process that was far simpler than that of the art and thus that had the profound advantages of saving both time and money.

The Examiner contends that since Applicants' specification indicates that methods of inserting complete cDNA sequences, into expression vectors were known, Applicants' process would have been obvious. Respectfully, this assertion overlooks the fact that one skilled in the relevant art would have concluded that, to produce a recombinant antibody, it would have been necessary to remove the 3' untranslated region of each sequence. As indicated above, for the heavy chain, this could only be achieved by removing the region encoding the constant region and replacing it with genomic DNA of the Ig class. For the light chain, this could be achieved by subjecting the sequence to the action of a restriction enzyme that would partially digest the sequence so as to remove the 3' end of the sequence, including the poly A

sequence. Fortuitously, Applicants found that the entire cDNA, including the polyadenylation sequence and preceding untranslated region, was suitable for human immunoglobulin expression with no further processing required, and without the necessity for genomic DNA sequences. This approach was in no way suggested by the art and thus the possible availability of methods to which the Examiner refers would have been of no consequence.

Reconsideration is requested.

Claims 3 and 6 stand rejected under 35 USC 103 as allegedly being obvious over Gillies et al in view of Foung et al and Ehrlich et al. This rejection is traversed.

The discussion of the inadequacies of the Gillies et al reference above is equally applicable to this rejection. The teachings of the secondary references cited by the Examiner are not sufficient to overcome these deficiencies. Neither Foung nor Ehrlich et al teach or suggest any method for producing recombinant antibodies, much less that a recombinant antibody could be produced by obtaining the cDNA encoding the entire constant and variable regions of each of the heavy and light chain of the antibody, inserting the cDNA into an expression

vector under the control of expression signals, transfecting a cell with the expression vector and then culturing the cell under antibody-producing conditions. Accordingly, reconsideration is requested.

Claim 11 stands rejected under 35 USC 103 as allegedly being obvious over Gillies et al in view of Larrick et al. Again, the deficiencies of the Gillies et al reference as set forth above, are equally applicable to this rejection. The secondary reference does not compensate for the deficiencies of the primary reference. As indicated above, Gillies et al teach that it is necessary to use genomic DNA as the source for part of the DNA encoding the constant region of the antibody chain. Larrick et al do not address this issue. They teach a method of amplifying human monoclonal antibody variable region genes using PCR and a mixture of upstream primers corresponding to the leader sequence and one downstream primer designed from the conserved nucleotide sequence of the constant region. The reference does not teach any primers which would enable the amplification and cloning of the entire gene including both the constant and variable regions. The combined teachings of these references do not teach or

suggest the method set forth in claim 11 of this application. Accordingly, reconsideration is requested.

This application is submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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